REMARKS

The withdrawal of the rejection of all claims over Ghebre-Sellassie in view of Krause and further in view of Deboeck is acknowledged. The Examiner is thanked for carful consideration of these rejections.

Claims 16 and 42 are amended to recite that the bioavailability is distinctly greater than that of the prior art form of fenofibrate tablets. The word "distinctly" refers to the fact that experimental comparison between the claimed composition and the reference product Lipanthyl is made and analyzed by a person skilled in the art and the resulting superiority should be significant (beyond the margins of error) and that the bioavailability is evaluated in conditions wherein all other parameters are equal (same set of individuals tested, same protocol of administration). This is sufficiently supported by the description (page 11, lines 16-17).

Claims 16 and 42 are also amended to further define the "co-micronized fenofibrate" to which the inventive composition is compared. Applicants submit that it is clear to a person skilled in the art that the expression "wherein the bioavailability is distinctly greater than that of 200 mg fenofibrate co-micronized with sodium lauryl sulfate" refers to a comparison to Lipanthyl 200M® as referred to in the claims of record. It is clear from the specification and the claims that this further definition of the comparative product is the same as Lipanthyl® 200M.

Claims 49 and 50 are sought to be added. The reference product Lipanthyl ®200M has been detailed in new claims 49 and 50 with reference to its generic description according to the application (page 11, lines 10-13), which is consistent with the description given in EP-0 330 532 and in Deboeck (co1.1, 1ines 46-52). However, the applicant believes that the description given in claim 16 is sufficiently detailed because a person skilled in the art (a chemist specialized in medicament formulation) who wants to evaluate a composition knows that he has to take as a reference the commercial Lipanthyl 200M® and there is no ambiguity with regards to that point. No new matter has been added.

Claim 51 and 52 are sought to be added. Claims 51 and 52 define specific parameters as defined in the application as originally filed. See, for example, page 4, lines 16-20.

Applicants submit that entry of the above amendments does not change the scope of the claims, but only further clarifies what is already present and places the claims in better condition for examination. Accordingly, entry of the amendments is proper.

With entry of this amendment, claims 16, 18-20, 36, 41-45, and 49-52 are under examination. Entry of these amendments and reconsideration is requested.

Claim Objections

Claims 6, 7, 13 and 14 are now cancelled. Accordingly, the objections should be withdrawn.

Rejections under 35 USC § 103

Claims 16, 18-20, 36 and 41-45 stand rejected as being obvious over Krause (U.S. Patent No. 4,859,703) in view of Deboeck (U.S. Patent No. 5,545,628). These rejections are traversed for the following reasons.

As explained more fully below, Krause and Deboeck are not combinable, a person skilled in the art would not be motivated to combine Krause and Debeock, and even if the combination could be or were made, one would not arrive at the present invention nor have a reasonable expectation of success.

The prior art:

Krause relates to pharmaceutical compositions comprising combinations of blood serum lipid and cholesterol regulating agents. The lipid regulating agent, e.g.fenofibrate, is administered in a dosage from 300 to 1200 mg per day. (Col. 5, lines 46-55) Examples 5 to 10 disclose immediate-release tablet formulations comprising 300, 450 or 600 mg of a lipid regulating agent which, among others, can be fenofibrate. Krause does not mention or address the problem of bioavailability of the active principle, in particular the problem of bioavailability of fenofibrate. In no event does Krause suggest that the dosage of fenofibrate can be lowered. The compositions taught by Krause also comprise another active principle, an ACAT inhibitor, which acts on cholesterol absorption by intestinal mucosal cells (co1.2, 1ines 36-45). Krause teaches mixing the lipid regulating agent and the ACAT inhibitor with the other excipients as powders, then granulating them with an aqueous solution of polysorbate.

Deboeck describes a pharmaceutical dosage form of fenofibrate having bioavailability similar to that of the prior art Lipanthyl 200 M® composition. It is said that the described formulation does not require the use of co-micronisation and "exhibits a bioavailability comparable to formulation of fenofibrate which do." (col. 2, lines 12-15, emphasis added). It is

also pointed out that an object of this reference is to provide a solid dosage form of fenofibrate that does not require any particle size specification. The compositions in Deboeck contain fenofibrate and an excipient chosen from one or more polyglycolized glycerides (col. 2, lines 16 to 26). The suspensions can have additional substances such as stabilizers chosen from cellulose derivatives (col. 2, lines 43 to 54).

Deboeck refers to the composition sold under the trade name Lipanthyl 200 M® (col. l, lines 46-57) and confirms that Lipanthyl 200 M® is formulated according to the teachings of EP-0 330 532. According to Deboeck, Lipanthyl 200 M® consists of fenofibrate powder co-micronized with sodium lauryl sulphate. This co-micronized powder is then mixed with excipients: lactose, starch, polyvinyl pyrrolidone and magnesium stearate.

Deboeck describes compositions which comprise fenofibrate and polyglycolized glycerides. The method for preparation of the capsules (melting) is such that the fenofibrate is in a liquid form in the capsule (col. 3, lines 40-48). It is taught by Deboeck that the excipient mixture of polyglycolized glycerides facilitates the absorption of fenofibrate by the stomach (col. 3, lines 40-48). The results relating to comparison of the bioavailablity with Lipanthyl 200M® are mentioned in the pharmacokinetic study, particularly in the comparison of example 2 (200 mg of fenofibrate according to the formulation of the Deboeck reference) with Lipanthyl 200M®. The results of Table 4 are in accordance with what is stated in col. 2: the bioavailability of the composition according to said reference is comparable to (not distinctly greater than) that of Lipanthyl 200M®.

It should be emphasized that the bioavailability study made by Deboeck illustrates what is common knowledge to the skilled professional: the bioavailability parameters vary with some conditions of test: here table 4 illustrates a variation in the bioavailability of fenofibrate when administered together with food as compared to an administration without food.

The present invention:

The aim of the compositions of the invention is to lower the amount of daily administered fenofibrate, while providing to the individual in need thereof an efficient quantity of fenofibrate. Neither Krause nor Deboeck, alone or in combination suggest these goals or disclose a composition that attains these improvements. Actually, when prior art formulations were administered, a large part of the fenofibrate was not assimilated by the patients. The

bioavailability of the active principle, here fenofibrate, reflects the capacity of the active principle to be assimilated by patients.

Bioavailability parameters (AUC, Cmax, Tmax, $T_{1/2}$) are not absolute parameters. Their value will depend on the physical properties of the drug, the excipients with which it is mixed, whether the drug is administered in a fed or a fasted state, the hour of the day at which the drug is administered, the presence of other active principles etc. This is common knowledge in the art and can be checked in any manual regarding bioavailability studies.

For example, reference is made to the Wikipedia encyclopedia chapter regarding bioavailability: http://en.wikipedia.org/wiki/Bioavailability which illustrates this knowledge. Section 4 entitled "Factors influencing bioavailability" is especially referred to.

Similar description is given in the document "Note for guidance on the investigation of bioavailability and bioequivalence" by the European Agency for the Evaluation of Medicinal products, a copy of which is attached for reference. This document clearly details the definitions of bioavailability and bioequivalence and states that "A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products... Since bioavailability studies are comparative in nature" (second paragraph of page 6), and further in §3.1 Design "The study should be designed in such a way that the formulation effect can be distinguished from other effects."

Also attached is a copy of the document Bioequivalence guidance from the FDA. This document gives definitions of the parameters Cmax and Tmax and indications with regards to the statistical analysis of data in the context of bioequivalence studies (p. 16-17).

The variation observed in the Deboeck study when comparing Lipanthyl administred with a meal or without a meal (table 4) is consistent with the statements contained in all these documents. Distinct test conditions give distinct bioavailability results.

Therefore, a person of ordinary skill in the art, a chemist with a good knowledge of medicament formulation, knows that a comparative bioavailability experimental study is conducted with all factors identical, except the factors which are the object of the comparison. At the time the present application was filed, the formulation based on fenofibrate which possessed the highest bioavailability was Lipanthyl 200M®.

The problem that the present inventors have solved is the improvement of fenofibrate bioavailability as compared to Lipanthyl 200M®. The result is a composition according to the

invention, with a daily dose lower than 200 mg and bioavailability superior to that of Lipanthyl 200M®.

Inventiveness:

The sole relationship between the Krause reference and the present invention is that Krause mentions use of fenofibrate, but this reference is of no interest for one skilled in the art, seeking to lower the daily prescribed amount of fenofibrate. Krause does not teach improving the bioavailability of fenofibrate; the compositions taught by Krause have a different effect because they also comprise another active principle, an ACAT inhibitor (see col. 2, lines 28-45). Consequently, in the compositions taught by Krause, if there even is an effect on the bioavailability of fenofibrate, it is due to significant disturbance by this ACAT inhibitor. It is all the more so that the ACAT inhibitor also acts on lipid metabolism, and therefore interferes with the mechanisms of action of other lipid regulating agents like fenofibrate. For this reason, a person skilled in the art who wanted to improve the bioavailability of fenofibrate would have considered Krause's teaching as totally inappropriate to attaining this goal.

While Deboeck is concerned with bioavailability of fenofibrate compositions, it does not teach or suggest a composition with bioavailability superior to that of then existing formulations. A person of ordinary skill in the art would never have combined the teachings of Deboeck with the teachings of Krause, which is not concerned with fenofibrate bioavailability and does not suggest that a dosage lower than 200 mg would be effective. Additionally, the skilled professional would not know how to combine the practical teachings of Deboeck and Krause with regards to formulation to arrive at the present invention. He would be tempted to use the excipients and method of preparation taught by Deboeck, because Deboeck explicitly mentions that these characteristics permit a better absorption of the fenofibrate, but he would not from such a melted mixture of fenofibrate and polyglycolyzed glycerides obtain a powder in order make a tablet according to the method illustrated in Krause's examples.

Accordingly, whether viewed from a theoretical point of view (considering the problem solved) or from a practical point of view (actual preparation of the medicament composition), the combination of Deboeck with Krause is not possible, or even if combined, a person of ordinary skill in the art would not expect a reasonable likelihood of success of producing a formulation with improved bioavailability.

Further, even if a person skilled in the art combined the teachings of Deboeck and Krause, he would not have obtained the invention as defined by the present claims. There is absolutely no reason to believe that making tablets from the Deboeck formulations (supposing that there is a method to transform a melted mixture into a tablet) would lead to an improvement of the bioavailability. On the contrary, it is clearly understandable from Deboeck that the specificities of his formulation method account for the satisfactory bioavailability. The results of Table 4 in the Deboeck document are in accordance with what is stated in col. 2: the bioavailability of the Deboeck composition according to said reference is only comparable to the one of Lipanthyl 200M®.

In contrast, the compositions of the invention offer a higher bioavailability in comparison with Lipanthyl 200M®. This is demonstrated in Table 1 of the present specification, where all parameters (C_{max}, T_{max}, $T_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$) show that the bioavailability of the composition of the invention is distinctly higher than the bioavailability of Lipanthyl 200M®. Based on the data presented in the present specification and in Deboeck, it can be derived that the compositions according to the invention have a superior bioavailability as compared to Deboeck, which is only comparable to Lipanthyl 200M®.

As a result, the compositions of the invention have been shown to have superior bioavailability as compared to the prior art compositions. The compositions of the invention permit the same therapeutic effect while administering far less amount of fenofibrate.

Applicants further submit that in view of the explanation above regarding bioavailability tests, no absolute value of AUC, Cmax, Tmax, $T_{1/2}$ need be included in the claims, because the values of AUC, Cmax, Tmax, or $T_{1/2}$ depend upon the set of individuals tested, and the protocol of administration. However, the evaluation of those parameters is routine to persons skilled in the art, as well as the analysis of results and their differences. Choosing a commercial product as a reference in a bioavailability test is the normal way of proceeding for the skilled professional.

Accordingly, Applicants submit that Krause fails to teach a fenofibrate formulation that contains less than 200 mg fenofibrate and has improved bioavailability. Although Deboeck teaches dosages under 200 mg fenofibrate, such forms are described as providing bioavailability comparable to and not distinctly greater than that of Lipanthyl 200M®. Thus, even if combined, the references do not teach the elements of the presently claimed invention. Additionally, because Krause and Deboeck describe significantly different formulations, a person having

ordinary skill in the art (a) would not be motivated to combine the references and (2) would not have a reasonable expectation of success of obtaining a formulation according to the present invention.

For each of these reasons, Applicants respectfully submit that the present rejections should be withdrawn and the claims allowed.

CONCLUSION

All the stated ground of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

The Commissioner is authorized to charge any deficiency in any patent application processing fees pursuant to 37 CFR § 1.17, including extension of time fees pursuant to 37 CFR § 1.17(a)-(d), associated with this communication and to credit any excess payment to Deposit Account No. 22-0261.

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Respectfully submitted,

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